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(54) **Pharmaceutical granulate containing steroids.**

(57) Disclosed is a process of preparing granules involving first preparing a carrier comprising diluent, binder, and optionally a disintegrating agent. In a container separate from said carrier, a steroid, lubricant and, optionally, an antioxidant are dissolved in an, optionally pre-heated, organic solvent. The resulting solution is added to the carrier contained within an, e.g vacuum mixer, followed by further blending of the mixture. The organic solvent is removed from the mixture. The mixture is blended further to form granules. The process may further include incorporating a flow enhancer such as colloidal silicon dioxide into the granules. A granule for making a pharmaceutical dosage unit is granule characterized in comprising: a) a carrier comprising diluent and binder, and b) a film coating said carrier, said film comprising desogestrel and a lubricant, and has the characteristic of by retaining 90% of the desogestrel at a pressure of 150 mbar and at a temperature of 70 ° C over 72 hours.

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This invention relates to pharmaceutical compositions generally, and more specifically to pharmaceutical granulates and processes for making them.

Methods for making tablets and other solid or dry pharmaceutical preparations are well-known. For example in the standard text Gennaro et al., Remington's Pharmaceutical Sciences, pp. 1633 - 1665 (18th ed. 1980, Mack Publ. Co. of Easton, PA, U.S.A.) ("Remington's"), methods of making tablets, capsules and pills and their respective components are described. Three methods of making tablets include the "wet-granulation", "dry-granulation", and direct compression methods.

Wet-granulation methods involve weighing out ingredients (including a solvent), mixing them, granulating them, screening them damp, drying them, dry screening, lubricating, and compressing the resultant admixture into tablets. See, e.g. Belgian Patent No. 773,064. Such procedures generally result in tablets having adequate tablet homogeneity.

While granules made according to these methods are adequate for many medicinal agents, they are not altogether adequate for use with certain medicinal agents and applications (e. g. for making tablets containing low doses of very potent steroids).

It has been found that certain steroids such as desogestrel transfer from tablets into the surrounding local environment. If the transfer of the steroid from the tablet cannot be prevented, the quantity of steroid contained within the dosage unit may drop below stated levels within a relatively short period of time.

In the present invention a simple inexpensive and unobvious new solution is provided for this problem. When both the steroid and a lubricant are dissoluted in an organic solvent, the granulate which can be prepared comprises a film coating (or matrix) consisting of said steroid and the lubricant. Surprisingly this film coating prevents the migration. For desogestrel very good results are obtained when stearic acid is applied as lubricant. The advantages of granules of this new type (non-migration granules) are clear, and such granules can easily be discerned from regular granules known in the art by measuring the migration properties of desogestrel from said granules.

The invention further includes a process of preparing granules which, among other things, display the ability to retain compounds such as desogestrel even under extreme conditions. The process involves first mixing a carrier comprising diluent, binder, and optionally a disintegrating agent. The carrier may be prepared in a mixer or alternatively in another container, and then added to the mixer. In a container separate from the container containing the carrier, a steroid or steroids, lubricant and, optionally, an antioxidant are dissolved in a suitable organic solvent. The resulting solution is added to the carrier which, if it is not already present, is transferred to the mixer. The carrier and solution are blended. The organic solvent is then removed (e.g. by evaporation), and the mixture further blended to form steroid loaded granules (i.e. granules containing steroid).

After removal of the organic solvent, the steroid loaded granules may be mixed with a flow enhancer such as colloidal silicon dioxide.

The resulting granules are remarkably homogenous, with the steroid or steroids being distributed evenly over the granules. Tablets made with the granules are very resistant to segregation. The procedure further results in a non-agglomerated drug. Micronized materials need not be used resulting in a simpler, more economic granulation process. Tablets made with the granules have excellent dissolution rates. The entire process is relatively easily scaled-up.

Various steroids can be used with the invention. Preferably the steroids used in the compositions and processes of the invention are estrogens, progestogens, or both of them. The process is of particular interest for apolar steroids.

Progestogens for use with the invention include apolar progestogens. Especially preferred is desogestrel.

Examples of preferred estrogens include ethinyl estradiol, mestranol and 17-α-ethinyl estradiol 3-methylether, ethyl estranol, and other compounds with estrogenic activity.

Granules according to the invention are made of a) a film coating the carrier, and preferably b) a carrier which comprises a diluent and a binder. The film coating is made of at least desogestrel and a lubricant distributed over the carrier. The granules, and pharmaceutical dosage units made with them, prevent transfer of the compound out of the dosage unit. As used herein, "transfer" includes any process in which the compound prematurely leaves the dosage unit.

Desogestrel containing granules made according to the invention have the characteristic of retaining more than 90%, preferably more than 95%, and even more preferably more than 97% of the desogestrel when stored at a pressure of 150 mbar, at a temperature of 70° C over 72 hours.

The granules are preferably used to make a stable solid pharmaceutical unit such as a tablet, capsule, pill, dragee, or powder. A coated biconvex tablet is the presently most preferred dosage unit. Tablets made with desogestel containing granules have the characteristic of retaining more than 90%, preferably more

than 95%, and even more preferably more than 98% of the desogestrel when stored at a pressure of 150 mbar, at a temperature of 70 ° C over 72 hours.

The term "dosage unit" or "pharmaceutical dosage unit" generally refers to physically discrete units suitable as unitary dosages for humans or animals, each containing a predetermined quantity of active material (e.g. estrogen or progestogen) calculated to produce the desired effect. Examples of such dosage units are tablets, capsules, powders, and pills.

Methods and compositions for making various dosage units using the granules are known to those skilled in the art. For example, methods and compositions for making tablets, capsules and pills using the granules are described in Remington's, at pages 1633 through 1665. Methods of coating pharmaceutical dosage units are described at pages 1666 to 1675 of the reference.

The concentration of steroid or steroids included in the granules - and eventually the dosage unit - will of course depend on the particular steroid's potency, its intended use, and the eventual mass of the dosage unit. The amount of a steroid or steroids used in a dosage unit will be well-known to those skilled in the art.

A carrier according to the invention is typically a basic granulate containing a diluent and binder. Preferably the carrier will also include a disintegrating agent.

Diluents or "filler excipients" are agents added to dosage units to increase the granules' and resulting dosage units' bulk. The preferred diluent for use in this regard is lactose. Other diluents include mannitol, sorbitol, cellulose, xylitol, dextrose, fructose, calcium phosphate, $NaCaPO_4$, sucrose, and mixtures thereof. The diluent will typically make up from 70 to 95% by weight of the resulting steroid loaded granules.

Binders are agents used to impart cohesive properties to the granules, resulting in more physically stable dosage units, and include hydroxypropylcellulose, amylopectin, starch, hydroxypropylmethylcellulose, gelatin, and starch based binders. The preferred binder for use with the invention is povidon (polyvinyl-pyrolidone). The binder will typically make up from 0.5 to 5% by weight of the resulting steroid loaded granules.

Disintegrating agent or "disintegrators" are substances or mixtures of substances added to a tablet to facilitate its breakup or disintegration after administration. Typically such agents are modified or unmodified starches, clays, cross-linked PVP, modified or unmodified celluloses, gums or algins. The presently most preferred agents are corn starch, potato starch, and wheat starch. Disintegrators will typically make up from 5 to 50%, preferably 5 to 15%, by weight of the resulting granules.

The carrier may be prepared in the mixer. This avoids unnecessary process steps, such as transferring the carrier to the mixer, thus also preventing possible waste. However, the carrier is preferably made in a fluidized bed granulator, and then later added to the mixer for later loading with steroid.

Mixers for use with the invention are readily commercially available and are capable of mixing or blending the dry ingredients with the organic solvent containing the steroid or steroids. Vacuum mixers which are closed to the outside environment are preferred for workers' safety and environmental reasons since the solvent is not released into the atmosphere, and can be collected for re-use. Vacuum mixers are like general mixers except they also typically have a heating jacket and vacuum connections. The production of a vacuum in the mixing environment allows for shorter drying times, lower drying temperatures, and for the exclusion of oxygen from the mixing process which may be useful for drugs which are sensitive to oxygen or heat.

The "wet" portion added to the carrier will preferably consist of the steroid or steroids, an antioxidant, and a lubricant all dissolved in an organic solvent.

Lubricants are agents which improve the rate of flow of the tablet granulation, prevent adhesion of the tablet material to the surface of dies and punches, reduce interparticle friction, and facilitate the ejection of the tablets from the die cavity. Commonly used lubricants are talc, long chain fatty acids, magnesium stearate, stearic acid, calcium stearate, polyethylene glycol, palmitic acid, and hydrogenated vegetable oils. The presently most preferred lubricant for use with the invention is stearic acid, or chemically related fatty acids such as palmitic acid. The lubricant will typically make up from 0.25 to 3% by weight of the resulting granules.

Organic solvents for use with the invention are preferably those having a sufficiently low boiling point at the pressures attainable in the vacuum mixture to evaporate off during the process. These include acetone, dichloromethane, ethanol, methanol, isopropanol, and mixtures thereof. The binder need not be very soluble in the organic solvent.

A sufficient amount of organic solvent will be used to dissolve the steroid or steroids, lubricant and antioxidant, and sufficiently wet the carrier without impairing the flow properties. Thus the amount of organic solvent used in the process will depend upon the potency and solubility characteristics of the particular steroid or steroids in the particular organic solvent, the solubility of the other components in the solvent, and the size of the batch of carrier to be wetted. Organic solvent will typically make up from 5 to 20% by weight

of the mixture of solution and carrier.

The organic solvent is preferably pre-heated to a temperature less than its boiling point. Such pre-heating increases the speed of dissolution of the lubricants, antioxidants, and steroid or steroids in the solvent; results in better distribution of the components over the carrier; and eases removal of the solvent from the granules. Heating of the solvent containing steroid and lubricant is also preferably maintained during its transfer to the mixer.

The carrier may also be pre-heated before addition of the wet portion to decrease the amount of time needed to evaporate the solvent.

After removal of the solvent, a flow enhancer is preferably mixed with the drug loaded granules. The flow enhancer (e.g. colloidal silicon dioxide) acts to prevent the granules from clumping. Flow enhancers will typically make up from 0.1 to 3% by weight of the resulting mixture.

The use of other conventional additives or "further excipients", e.g. colorants, stabilizers or antioxidants, is contemplated. Stabilizers such as EDTA, polyethylene glycol (PEG), and butylated hydroxytoluene (BHT), may also be included if desired, although it is not required. The presently most preferred antioxidant for use with the invention is dl-α-tocopherol. Other medicinal agents (e.g. 17β-estradiol) may also be included in the formulation.

The granules may then be tabletted or encapsulated by means well-known to those skilled in the art. Tablets made with granules of the invention allow for much less transfer of desogestrel from the tablets than do tablets containing desogestrel made according to prior art techniques.

The invention is further explained by reference to the following illustrative examples:

EXAMPLE I

Dosage units (tablets) containing:

Excipients:	
Desogestrel	150 µg
EE	30 µg
PVP	2.4 mg
Stearic acid	0.8 mg
Corn starch	6.5 mg
Colloidal SiO_2	0.8 mg
dl-α-tocopherol	0.08 mg
Lactose 100 M	67.74 mg

were made by the following process.

Tablets were made by first preparing the carrier. In a vacuum mixer, 4880 g of carrier components (87% lactose, 10% corn starch, and 3% PCP) were added. The components were mixed and heated to 35 °C. In a separate container, desogestrel (11.54 g), ethinyl estradiol (2.31 g), stearic acid (50.0 g), dl-α-tocopherol (6.17 g) were dissolved in 350 ml of acetone, pre-heated to 45 °C. This solution was then mixed with the carrier in a vacuum mixer (kept at 100 mbar). The beaker containing the acetone solution was then rinsed with acetone, and the wash solution transferred to the mixer. The mixture was blended for 10 min, the mass heated to a temperature of 45 °C, corresponding to a jacket temperature of 47 °C. Blending was stopped, and the mass allowed to cool to 15 °C. The vacuum was gradually adjusted to less than 25 mbar and the mass heated to a temperature of 45 °C, while blending continuously in order to evaporate the acetone. The mixture was further blended without heating until the mass reached a temperature of 20 °C forming drug loaded granules.

50g of colloidal SiO_2 was then transferred to the mixer.

Blending (min.)	Position	Rotation Speed (rpm)	Direction
1	90°	ca. 14	left
0.5	ca. 120°	ca. 14	left
1	90°	ca. 14	right
0.5	ca. 45°	ca. 14	right

The resulting mixture was compressed on a rotary press to biconvex tablets. The tablet weight was adjusted to 65 mg.

EXAMPLE II

The granules and tablets of EXAMPLE I were compared with the following tablets each containing:

Desogestrel (micronized)	150 µg
EE (micronized)	30 µg
Na starch glycolate	1.2 mg
Colloidal SiO_2	0.9 mg
Mg Stearate	0.3 mg
Spray-dried lactose (Pharmatose DCL-11) qsad	60.0 mg

These tablets were made by first dry mixing desogestrel and EE with proportionate quantities of spray dried lactose for approx. 3 min. The other ingredients were then also mixed into the mixture until for approx. 5 min. The mixture was then tabletted by direct compression.

The tablets were subjected to various conditions wherein the transfer of drug from the granule or tablet could be measured, with the following results:

A. Transfer from dosage unit

Subject	percentage remaining (weight)
EXAMPLE I	
Granules	97
Tablets	98
EXAMPLE II	
Granules	67
Tablets	87
Conditions: stored for 72 hours at a pressure of 150 mbar, at a temperature of 70 ° C	

B. Transfer to Packaging material

These tablets of this EXAMPLE II and the tablets of EXAMPLE I were coated with:

Hydroxypropylmethyl-cellullose E 15	0.75 mg
PEG 400	0.15 mg
Talc	0.19 mg
Titanium dioxide	0.11 mg
Demineralized H_2O	to 15 µl

Both sets of tablets were packaged in PVC/aluminum foil packs, and subjected to a test to examine the extent of transfer of desogestrel from the coated tablets to the packaging material.

Tablets made according to EXAMPLE I, and coated, lost less than 0.5% of their total steroid content to the surrounding PVC material after even 19 months of storage at 32 °C and 70 % relative humidity. In contrast, coated tablets made as per this EXAMPLE II displayed 12.4% transfer to the packaging material after only 6 months at 37 °C and ambient relative humidity, and 16.2% after 6 months at 37 °C and at 95% relative humidity. Surprisingly, even coating of the dosage unit does not prevent migration of desogestrel.

EXAMPLE III

Content Uniformity

The content uniformity of desogestrel and EE in tablets prepared according to EXAMPLE I was determined and revealed relative standard deviations of approximately 1% (0.5 to 1.5%) indicating excellent homogeneity of the steroids throughout the tablets.

EXAMPLE IV

Segregation Stability

A sample of granulate made according to EXAMPLE I was sieved using the following sieves: -0, 75, 90, 150, 300, and 500 µm. From the different particle ranges the content of the active ingredients was determined, as was the weight fraction. The demixing potential (DP%) was calculated for the sample using the following formula:

$$DP\% = \frac{100}{\bar{p}} \left[\sum_{i=1}^{n} \frac{w_i}{100} (p_i - \bar{p})^2 \right]^{\frac{1}{2}}$$

wherein p_i is the proportion of drug associated with w_i weight% of the mixture in sieve fraction i. The mean content was determined by:

$$\bar{p} = \frac{\sum_{i=1}^{n} p_i * w_i}{\sum_{i=1}^{n} w_i}$$

The calculated demixing potential for ethinylestradiol and desogestrel were 8.17% EE and 8.42% desogestrel, both well under the safety limit of 10%, and indicating a high stability against segregation explaining the high content uniformity shown in EXAMPLE III.

EXAMPLE V

Capsules are made by incorporating the "Excipients" portion of EXAMPLE I into capsules.

Claims

1. A process for preparing steroid loaded granules comprising:
   a) dissolving a steroid and a lubricant in a sufficient amount of an organic solvent to form a solution;
   b) mixing the solution with a carrier comprising diluent and binder thus forming a mixture of solution and carrier; and
   c) removing the organic solvent from the mixture while blending the mixture to form steroid loaded granules.

2. The process according to claim 1 wherein said organic solvent is removed in a vacuum mixer.

3. The process according to claim 1 or 2 wherein said steroid is desogestrel.

4. The process according to any one of claims 1-3 wherein said lubricant is stearic acid.

5. A granule for making a pharmaceutical dosage unit, obtainable by the process of claim 1, characterized in that it contains a film coating comprising a steroid and a lubricant.

6. The granule of claim 5, characterized by comprising desogestrel and stearic acid, and further characterized by retaining 90% of the desogestrel within said granule at a pressure of 150 mbar and at a temperature of 70° C over 72 hours.

7. The granule of claim 5 or 6, characterized by comprising:
   a) a carrier comprising lactose, polyvinylpyrrolidone, and disintegrating agent; and
   b) a film coating said carrier, said film comprising desogestrel and stearic acid.

8. A tablet characterized by comprising the granule of any one of claims 5-7.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 93 20 3476

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
Y	WO-A-93 13760 (GERGELY, GERHARD) * claims 1,2,4 * * page 3, line 4 - line 11 * * page 4, line 6 - line 17 *	1,2,4,5,8	A61K9/16 A61K9/20
Y	US-A-4 180 560 (MARTIN KATZ ET AL.) * claim 1 * * column 4, line 19 - line 25 * * column 4, line 51 - line 54 * * column 6, line 15 - line 29 * * column 7, line 8 - line 13 *	1,2,4,5,8	
A	EP-A-0 491 443 (AKZO N.V.) * example 1 *	3,7	

TECHNICAL FIELDS SEARCHED (Int.Cl.6)

A61K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	10 May 1994	Ventura Amat, A

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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